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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Appl. No. : 10/564,823
Applicant : STEIN et al
Filed : April 18, 2006
TC/A.U. : 1645
Examiner :

Docket No. : 2958-135
Customer No.: 6449
Confirmation No.: 2061

SUBMISSION OF INTERNATIONAL PRELIMINARY REPORT

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

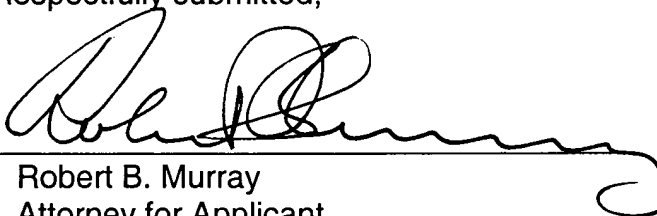
Dear Sir:

Submitted herewith is a copy of the translation of the International Preliminary Report.

In the event that any fees are due with this paper, please charge our Deposit Account No. 02-2135.

Respectfully submitted,

By



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RBM/cb

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF TRANSMITTAL
OF COPIES OF TRANSLATION
OF THE INTERNATIONAL PRELIMINARY REPORT
ON PATENTABILITY
(CHAPTER I OR CHAPTER II
OF THE PATENT COOPERATION TREATY)
(PCT Rules 44bis.3(c) and 72.2)

To:

BOEHMERT & BOEHMERT
München

KRAUSS, Jan, B.
Boehmert & Boehmert
Pettenkoferstrasse 20/22
80336 München
ALLEMAGNE

16. Juni 2006

Gesehen: Serv: *sd* Anw.:

Verfügung:

Frist:

Date of mailing (day/month/year)
- 08 June 2006 (08.06.2006)

Applicant's or agent's file reference
U30057PCT

IMPORTANT NOTIFICATION

International application No.
PCT/EP2004/008053

International filing date (day/month/year)
19 July 2004 (19.07.2004)

Applicant

CHARITÉ-UNIVERSITÄTS- MEDEZIN BERLIN et al

1. Transmittal of the translation to the applicant.

The International Bureau transmits herewith a copy of the English translation of the international preliminary report on patentability (Chapter I).



The International Bureau transmits herewith a copy of the English translation of the international preliminary report on patentability (Chapter II).

2. Transmittal of the copy of the translation to the designated or elected Offices.

The International Bureau notifies the applicant that copies of that translation have been transmitted to the following designated or elected Offices requiring such translation:

None

The following designated or elected Offices, having waived the requirement for such a transmittal at this time, will receive copies of that translation from the International Bureau only upon their request:

AE, AG, AL, AM, AP, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EA, EC, EE, EG, EP, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OA, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW

3. Reminder regarding translation into (one of) the official language(s) of the elected Office(s).

The applicant is reminded that, where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary report on patentability (Chapter II).

It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned within the applicable time limit (Rule 74.1). See Volume II of the PCT Applicant's Guide for further details.

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Authorized officer

Agnes Wittmann-Regis

Facsimile No.+41 22 740 14 35

Facsimile No.+41 22 338 89 70

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter I of the Patent Cooperation Treaty)

(PCT Rule 44bis)

Applicant's or agent's file reference U30057PCT	FOR FURTHER ACTION		See item 4 below
International application No. PCT/EP2004/008053	International filing date (<i>day/month/year</i>) 19 July 2004 (19.07.2004)	Priority date (<i>day/month/year</i>) 18 July 2003 (18.07.2003)	
International Patent Classification (8th edition unless older edition indicated) See relevant information in Form PCT/ISA/237			
Applicant CHARITÉ-UNIVERSITÄTS- MEDEZIN BERLIN			

1. This international preliminary report on patentability (Chapter I) is issued by the International Bureau on behalf of the International Searching Authority under Rule 44 *bis*.1(a).

2. This REPORT consists of a total of 11 sheets, including this cover sheet.

In the attached sheets, any reference to the written opinion of the International Searching Authority should be read as a reference to the international preliminary report on patentability (Chapter I) instead.

3. This report contains indications relating to the following items:

- | | | |
|-------------------------------------|--------------|---|
| <input checked="" type="checkbox"/> | Box No. I | Basis of the report |
| <input type="checkbox"/> | Box No. II | Priority |
| <input checked="" type="checkbox"/> | Box No. III | Non-establishment of opinion with regard to novelty, inventive step and industrial applicability |
| <input type="checkbox"/> | Box No. IV | Lack of unity of invention |
| <input checked="" type="checkbox"/> | Box No. V | Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement |
| <input type="checkbox"/> | Box No. VI | Certain documents cited |
| <input type="checkbox"/> | Box No. VII | Certain defects in the international application |
| <input checked="" type="checkbox"/> | Box No. VIII | Certain observations on the international application |

4. The International Bureau will communicate this report to designated Offices in accordance with Rules 44bis.3(c) and 93bis.1 but not, except where the applicant makes an express request under Article 23(2), before the expiration of 30 months from the priority date (Rule 44bis .2).

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland Facsimile No. +41 22 740 14 35	Date of issuance of this report 29 May 2006 (29.05.2006)
	Authorized officer Agnes Wittmann-Regis Telephone No. +41 22 338 89 70

PATENT COOPERATION TREATY

Translation

From the
INTERNATIONAL SEARCHING AUTHORITY

PCT

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43bis.1)

To:

Date of mailing
(day/month/year)

Applicant's or agent's file reference
U30057PCT

FOR FURTHER ACTION
See paragraph 2 below

International application No. PCT/EP2004/008053	International filing date (day/month/year) 19.07.2004	Priority date (day/month/year) 18.07.2003
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International Patent Classification (IPC) or both national classification and IPC

Applicant
CHARITÉ-UNIVERSITÄTS- MEDEZIN BERLIN

1. This opinion contains indications relating to the following items:

- | | | |
|-------------------------------------|--------------|--|
| <input checked="" type="checkbox"/> | Box No. I | Basis of the opinion |
| <input type="checkbox"/> | Box No. II | Priority |
| <input checked="" type="checkbox"/> | Box No. III | Non-establishment of opinion with regard to novelty, inventive step and industrial applicability |
| <input type="checkbox"/> | Box No. IV | Lack of unity of invention |
| <input checked="" type="checkbox"/> | Box No. V | Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement |
| <input type="checkbox"/> | Box No. VI | Certain documents cited |
| <input type="checkbox"/> | Box No. VII | Certain defects in the international application |
| <input checked="" type="checkbox"/> | Box No. VIII | Certain observations on the international application |

2. FURTHER ACTION

If a demand for international preliminary examination is made, this opinion will be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1bis(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA/EP	Authorized officer
Facsimile No.	Telephone No.

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

International application No.

PCT/EP2004/008053

Box No. I Basis of this opinion

1. With regard to the language, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.
☐ This opinion has been established on the basis of a translation from the original language into the following language
_____, which is the language of a translation furnished for the purposes of international search (under Rule 12.3 and 23.1(b)).
2. With regard to any nucleotide and/or amino acid sequence disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:
 - a. type of material
☒ a sequence listing
☐ table(s) related to the sequence listing
 - b. format of material
☒ in written format
☒ in computer readable form
 - c. time of filing/furnishing
☐ contained in the international application as filed.
☐ filed together with the international application in computer readable form.
☐ furnished subsequently to this Authority for the purposes of search.
3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table(s) relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.
4. Additional comments:

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

International application No.

PCT/EP2004/008053

Box No. III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

- ☐ the entire international application
- ☒ claims Nos. 18 (in part), 14-16, 19-22 (IA)

because:

- ☒ the said international application, or the said claims Nos. 14-16, 19-22 (IA)
relate to the following subject matter which does not require an international preliminary examination (*specify*):

see Supplemental sheet

- ☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. _____
are so unclear that no meaningful opinion could be formed (*specify*):

- ☐ the claims, or said claims Nos. _____ are so inadequately supported
by the description that no meaningful opinion could be formed.

- ☒ no international search report has been established for said claims Nos. 18 (in part)

- ☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

- | | |
|----------------------------|--|
| the written form | <input type="checkbox"/> has not been furnished |
| | <input type="checkbox"/> does not comply with the standard |
| the computer readable form | <input type="checkbox"/> has not been furnished |
| | <input type="checkbox"/> does not comply with the standard |

- ☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-bis of the Administrative Instructions.

- ☐ See Supplemental Box for further details.

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.
PCT/EP2004/008053

Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability;
citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims	4, 7-24	YES
	Claims	1-3, 5, 6	NO
Inventive step (IS)	Claims	4, 7-24	YES
	Claims	1-3, 5, 6	NO
Industrial applicability (IA)	Claims	1-13, 17-18, 23-24	YES
	Claims		NO

2. Citations and explanations:

1. Reference is made to the following documents:

- D1: DATABASE EMBL 28 April 2003 (2003-04-28),
INTERNATIONAL HUMAN GENOME SEQUENCING
CONSORTIUM: "The DNA sequence of Homo
sapiens: "similar to expressed sequence
AI594717 [Homo sapiens]" XP002305044 Database
accession no. XM_294213
- D2: DATABASE Geneseq [online] 25 February 2003
(2003-02-25), "Human liver single exon probe,
SEQ ID No 20133." XP002305045, found in EBI
accession no. GSN:ABS45143 Database accession
no. ABS45143
- D3: DATABASE Geneseq [online] 2 August 2002
(2002-08-02), "Human colon cancer related
nucleotide sequence SEQ ID NO:2340"
XP002305046, found in EBI accession no.
GSN:ABQ58645 Database accession no. ABQ58645
- D4: OTSUKA et al. "Differential expression of the
L-plastin gene in human colorectal cancer
progression and metastasis" Biochem. Biophys.
Res. Comm. vol. 289, pages 876-881, 2001,
XP002237813

2. Novelty (PCT Article 33(2)) :

The subject matter of claims 1, 2, 5 and 6 is not novel with regard to D1. D1 discloses a nucleotide sequence which is more than 95% identical to SEQ ID NO: 1 (100% from nucleotide 116 to nucleotide 2559). The sequence is therefore considered to be a derivative of the nucleic acid sequence specified in SEQ ID NO: 1 and, consequently, is prejudicial to the novelty of claims 1(c), 5 and 6.

Claim 3 relates to an oligonucleotide which hybridizes specifically to a nucleic acid sequence according to claim 1. Since the claim does not specify the length of the oligonucleotide and the hybridization conditions, it comprises also very short oligonucleotides, including *inter alia* commercially available short linkers (see, for example, EcoR I linkers from Stratagene), which hybridize with the nucleic acid sequence according to claim 1 under less stringent conditions. Reference is moreover made to D2 (Database ABS45143; WO 0157273) which discloses *inter alia* an oligonucleotide of 206 bp in length (SEQ ID NO: 20133) which is 93% identical to SEQ ID NO:1 within a 193 bp overlap. This DNA molecule consequently also meets the requirements of claim 3. The subject matter of claim 3 is therefore not novel.

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

International application No.

PCT/EP2004/008053

Box No. V

Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

The remaining claims are considered novel because the use of the nucleotide sequence disclosed in D1 as a diagnostic or therapeutic agent has not been disclosed in the prior art.

3. Inventive step (PCT Article 33(3)):

D4 is considered to be the closest prior art. D4 describes differential expression of the L-plastin gene in colon cancer patients. Expression of the gene correlates in a significant manner with progression of the cancer and is a potential metastatic marker.

The present application differs from D4 in that another differentially expressed gene was identified which may be used for the diagnosis and therapy of tumors, in particular colon carcinomas. 7a5 was also shown to correlate with distant metastasizing; for example, 7a5 is expressed in distant metastases at a higher level than in primary tumors, and there is also higher expression in metastasizing primary tumors than in non-metastasizing tumors.

The problem on which the present application is based is therefore considered that of providing a gene suitable for detection and prognosis of distant metastases of colon carcinomas. The problem was solved by identifying the marker gene 7a5 according to the examples.

D3 discloses nucleic acid sequences which are differentially expressed in cancer cells and

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

International application No.

PCT/EP2004/008053

Box No. V

Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability;
citations and explanations supporting such statement

normal cells. The DNA sequences and the encoded protein are suitable for the diagnosis of early stages of colon carcinomas. One of the numerous sequences (SEQ ID NO: 2340) corresponds to the 5' end of the prognostin gene of the present application.

There is no indication in the prior art of the 7a5 gene being a suitable marker for predicting the metastasizing of colon carcinomas. D3 depicts the partial sequence of SEQ ID NO: 1 merely as one of many possible marker sequences for the early diagnosis of colon cancer. A person skilled in the art would therefore have no reason to select the sequence corresponding to the 7a5 gene. In contrast to already known marker genes for colon carcinoma, the particular expression pattern of the 7a5 gene appears to render the latter especially suitable for the prognosis, diagnosis and therapy of distant-metastasizing tumors. An inventive step can therefore be acknowledged.

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

International application No.

PCT/EP2004/008053

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

1. The internal name for the protein according to the invention, "7a5/prognostin", does not contain any technical information and is therefore not suitable for defining the protein in the independent claims (PCT Article 6). The protein, or the coding nucleic acid sequence, should be defined in the claims by referring to the specific sequence (SEQ ID NO).
2. Claims relating to a biological activity of 7a5/prognostin lack clarity (see claim 1(c)). The application does not contain any information at all on an actual or even only a suspected biological activity of the protein. The protein was merely shown to be overexpressed in particular tumors and metastases.
3. Claims relating to the diagnosis or therapy of tumoral diseases in general lack sufficient disclosure (PCT Article 5). The description discloses only differential expression of the gene in colon carcinomas and in distant metastases of said colon carcinomas. It does not demonstrate that the 7a5 gene is also overexpressed in other tumors and thus is suitable for the diagnosis and treatment thereof.

The subject matter of claim 21 concerning the use of the nucleic acid according to the invention as marker for genetic diseases also lacks sufficient

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.

PCT/EP2004/008053

Box No. VIII

Certain observations on the international application

disclosure. The 7a5 gene was not shown to
correlate with any genetic disease.

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/EP2004/008053

Supplemental Box

In case the space in any of the preceding boxes is not sufficient.

Continuation of:

Box III

1. Claim 18 includes the step of formulating a substance to be identified into a pharmaceutically acceptable form. Since the application does not disclose any substances binding to 7a5/prognostin other than antibodies, the subject matter of claim 18 was searched only as far as it is supported by the description, i.e. if the substance identified is an antibody to the 7a5/prognostin protein. Accordingly, the preliminary examination is restricted to the searched subject matter.
2. Claims 14-16 and 19-22 relate to subject matter which, in the opinion of this Authority, falls under PCT Rule 67.1(iv). Consequently, no expert opinion has been established in respect of the industrial applicability of the subject matter of said claims (PCT Article 34(4)(a)(i)).
The PCT Contracting States do not have uniform criteria for assessing the industrial applicability of claims 14-16 and 19-22 in their present form. Patentability may also depend on the wording of the claims. The EPO, for example, does not recognize the industrial applicability of claims to the medical use of a compound; it may, however, allow claims to the first medical application of a known compound or to the use of such a compound in the manufacture of a drug for a new medical application.